Annual Surveillance Summary: *Escherichia coli (E. coli)* Infections in the Military Health System (MHS), 2015

NMCPHC-EDC-TR-187-2017

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14. ABSTRACT
The EpiData Center (EDC) conducts routine surveillance of Escherichia coli among all beneficiaries seeking care within the Military Health System (MHS). This report describes demographics, clinical characteristics, prescription practices, and antibiotic resistance patterns in calendar year (CY) 2015. Multiple data sources were linked to assess descriptive and clinical factors related to E. coli. Overall, 2015 incidence rates (IRs) of E.coli in the MHS beneficiary and Department of Defense (DOD) active duty populations are increasing. Incidence among females was nearly 11 times higher than among males. The highest IR occurred outside the continental United States (OCONUS) (1,057.7 infections per 100,000 persons per year). Aligning with United States trends, most infections were found in the urinary tract (96.2%) and outpatient setting (97.7%). Drug-resistant E. coli comprised 20.7% of all E. coli infections. Nitrofurantoin and ciprofloxacin were the most commonly prescribed antibiotics. Department of the Navy (DON) deployment-related infections accounted for 0.2% of prevalence infections, the majority of which were females aged 18-24 years.

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Abstract

The EpiData Center (EDC) conducts routine surveillance of *Escherichia coli* among all beneficiaries seeking care within the Military Health System (MHS). This report describes activity in calendar year (CY) 2015.

Health Level 7 (HL7)-formatted microbiology data identified *E. coli* infections, demographics, clinical characteristics, seasonal activity, and antibiotic resistance patterns. Infections were matched to HL7-formatted pharmacy data to assess prescription practices, the Standard Inpatient Data Record (SIDR) to determine healthcare-associated exposures, Defense Manpower Data Center (DMDC) rosters to determine burden among Department of Defense (DOD) active duty (AD) members, and the DMDC Contingency Tracking System (CTS) to determine Department of the Navy (DON) deployment-related infections.

Overall, 2015 incidence rates (IRs) of *E.coli* in the MHS beneficiary and DOD active duty populations are increasing. Incidence among females was nearly 11 times higher than among males. The highest IR occurred outside the continental United States (OCONUS) (1,057.7 infections per 100,000 persons per year). Aligning with United States (US) trends, most infections were found in the urinary tract (96.2%) and outpatient setting (97.7%). Drug-resistant *E. coli* comprised 20.7% of all *E. coli* infections. Nitrofurantoin and ciprofloxacin were the most commonly prescribed antibiotics. DON deployment-related infections accounted for 0.2% of prevalence infections, the majority of which were females aged 18-24 years.

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Background

The genus *Escherichia* consists of five species, of which *Escherichia coli* (*E. coli*) is the most frequently identified and clinically important. The organism belongs to the Enterobacteriaceae family and is the most common aerobic, gram-negative rod bacteria found in the gastrointestinal (GI) tract.[1] Although most infections are endogenous, several variants of *E. coli* have been described that cause infections of the GI system (e.g., intestinal pathogenic *E. coli*) while others cause infections outside of the GI system (e.g., extraintestinal pathogenic *E. coli*).[2] This report focuses on extraintestinal pathogenic *E. coli* (ExPEC) infections and uses the terms ExPEC and *E. coli* interchangeably.

ExPEC are associated with a variety of diseases including gastroenteritis, urinary tract infections (UTIs), meningitis, and sepsis.[1,3] ExPEC is the most common cause of UTIs in humans and is the leading cause of enteric and systemic infections including bacteremia, nosocomial pneumonia, cellulitis, cholecystitis, osteomyelitis, infectious arthritis, cholangitis, and neonatal meningitis.[4-6] Due to the variety of illnesses in which the organism can manifest itself, and the mechanisms through which it causes disease, a direct seasonal correlation has yet to be determined.[7] However, peaks in infections during the summer months have been reported in the literature for foodborne and secondary blood stream infections (BSIs).[7,8] Global morbidity and mortality rates due to ExPEC infections are substantial and increasing.[9] Each year in the United States (US), ExPEC infections range in frequency from 6 to 8 million cases of uncomplicated cystitis to 127,500 cases of sepsis.[10]

A broad range of antimicrobial agents effectively inhibit the growth of *E. coli*. Cephalosporins, fluoroquinolones, and trimethoprim-sulfamethoxazole are first-line agents often used to treat community and hospital infections caused by *E. coli*. Carbapenems are widely accepted as the standard for empiric treatment of severe infections caused by extended-spectrum β-lactamases (ESBLs)-producing and AmpC-producing *E. coli*.[11] However, managing infections caused by ExPEC has been complicated by the emergence of resistance to first-line antimicrobials.[12]

ExPEC isolates display considerable genome diversity and have a wide range of virulence-associated factors including adhesions, toxins, lipopolysaccharides, polysaccharide capsules, invasins, and proteases which increase the organism's adaptability, competitiveness, and ability to colonize the human body.[11,13] Through this variety of resistance mechanisms, strains of *E. coli* have become resistant to a number of available antibiotics.[14, 15]

Until the 1990s, ExPEC infections were relatively susceptible to first-line antibiotics; however, since then, the medical community has observed an increase in ExPEC infections that are resistant to many first-line antibiotics, such as cephalosporins, fluoroquinolones, and trimethoprim-sulfamethoxazole.[16] Researchers at the Center for Disease Dynamics, Economics & Policy (CDDEP) documented a steady increase from 1999-2014 in drug-resistant *E. coli* across 39 countries.[17] In 1999, *E. coli* drug resistance to cephalosporins (third generation), carbapenems, and fluoroquinolones in the US were reported at 2%, 0%, and 5%, respectively. However, by 2014, resistance to these antibiotic classes rose to 16%, 1%, and 35%, respectively.[17] Other surveillance studies during the 2000's across Europe, North, and South

America show that between 20-55% of ExPEC infections are resistant to first-line antibiotics.[11,12,18]

Carbapenem-resistant Enterobacteriaceae (CRE) are unique among multidrug-resistant organisms (MDROs) because they are resistant to all or nearly all antibiotics available today, resulting in wide-ranging global public health implications. Bacterial genes responsible for carbapenem-resistance typically confer other resistance factors as well, resulting in a variety of resistance patterns.[7] The rising prevalence in multidrug-resistant (MDR) *E. coli* is a cause for concern and has major implications for selection of adequate empiric treatment.

In 2014, the HAI Prevalence Survey project documented the burden of healthcare-associated infections (HAIs) in US hospitals and reported that there were approximately 722,000 HAIs in US acute care hospitals each year, of which 75,000 resulted in death and cost $28-$45 billion annually.[19,20] From 2011-2014, the Centers for Disease Control and Prevention's (CDC) National Healthcare Safety Network (NHSN) indicated that *E. coli* accounted for 15% of all HAI pathogens.[21] In addition, *E. coli* has been identified as a causal agent of healthcare-associated UTIs, surgical site infections (SSIs), and BSIs among intensive care unit patients.[22]

In 2002, in the early phases of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF), bacterial infections were observed primarily in non-US or coalition patients seeking care at military treatment facilities (MTFs).[23] Throughout these conflicts, from 2002 to 2005, *E. coli* was increasingly isolated in service members suffering from gastroenteritis and war wound infections.[24] Since the beginning of combat in Afghanistan and Iraq, the US military healthcare system has dealt with a steady increase in resistant organisms isolated from wounded service members, comparable to experiences during international disaster relief and humanitarian missions.[23,25-28] Sources of these multidrug-resistant organisms have been postulated to include inoculation of the wound with host normal flora at the time of injury, wound contamination with water or soil organisms, or nosocomial transmission at local MTFs.[29] Previous studies identified that colonized local Afghani patients as the likely source of cross-contamination in deployed US hospitals.[27, 30]

It is important, therefore, to monitor *E. coli* trends on an ongoing basis. This analysis presents an annual update for calendar year (CY) 2015 of *E. coli* infection burden among Military Health System (MHS) beneficiaries. This report describes the demographics, clinical characteristics, prescription practices, and antibiotic susceptibility patterns for *E. coli* infections among MHS beneficiaries.

Methods

The EpiData Center (EDC) at the Navy and Marine Corps Public Health Center (NMCPHC) conducted retrospective surveillance of *E. coli* infection in the MHS in CY 2015 (01 January 2015 to 31 December 2015). Health Level 7 (HL7)-formatted Composite Health Care System (CHCS) microbiology data was used to identify positive *E. coli* laboratory results. A unique *E. coli* infection was defined as the first positive *E. coli* laboratory result per person per 30 days. Incidence represented the first unique infection per person per calendar year and prevalence was defined as all unique *E. coli* infections.

Demographic Classification

Demographic information for each incident infection was described using data within the HL7-formatted CHCS microbiology record and infections were classified according to the patient's gender, age, sponsor service (Air Force, Army, Marine Corps, or Navy), duty status (Active Duty, Retired, Family Member, or Other), and region of the facility where the specimen was collected. The Active Duty category included both active duty and recruit personnel, defined by the beneficiary type codes of 11 and 13, respectively.

E. coli incidence rates and prevalence infections were aggregated into six spatial regions and visualized as maps created in ESRI ArcGIS software (version 10.2.2). Organisms identified in each region may act as a reservoir within that region and contribute to the burden of exposure. Geographic regions were assessed within the continental United States (CONUS) and outside the CONUS (OCONUS), with the spatial regions identified as follows:

- **Northeast**: Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, Pennsylvania, New Jersey.
- **Midwest**: Michigan, Wisconsin, Minnesota, Ohio, Indiana, Illinois, Iowa, Missouri, Kansas, Nebraska, North Dakota, South Dakota.
- **West**: California, Oregon, Washington, Idaho, Montana, Wyoming, Colorado, New Mexico, Arizona, Utah, Nevada, Alaska, Hawaii.
- **South**: Texas, Oklahoma, Arkansas, Louisiana, Mississippi, Alabama, Tennessee, Kentucky.
- **South Atlantic**: Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia, Florida.
- **OCONUS**: All US territories and non-US countries.[31]

Clinical Characteristics Classification

Clinical characteristics were described for prevalent infections using information within the HL7-formatted CHCS microbiology record. Specimens were classified as inpatient or outpatient based on the Medical Expense and Performance Reporting System (MEPRS) codes of the location where the specimen was collected. A MEPRS code of A indicated specimen collection in the inpatient setting. All other MEPRS codes were considered outpatient encounters.

Infections were classified into invasive and non-invasive categories using the specimen source or body site variables in the HL7-formatted CHCS microbiology record. The terms used to group the data into these categories are described in Table 1. In addition, infections were further categorized based on body collection sites specific to the organism of interest (e.g., urine, respiratory, bloodstream) to provide enhanced granularity to the source of infection. Clinical characteristics were presented as a proportion of all infections within the population meeting the definition criteria.

Table 1. Invasive and Non-Invasive Infection Classification for *E.coli* Infections Accessing the MHS

Infection Classification	If Body Site or Specimen Source Sample Taken From:
Invasive Infections	Blood, bone, cerebrospinal fluid, peritoneal fluid, pleural fluid, or synovial fluid
Other Non-Invasive Infections	Abscess, aspirate, body fluid, boil, bursa, carbuncle, cellulitis, cyst, discharge, drainage, exudate, eye, genital, lesion, pus, pustule, respiratory, skin, sputum, stool, swab, throat, tissue, urine, or wound

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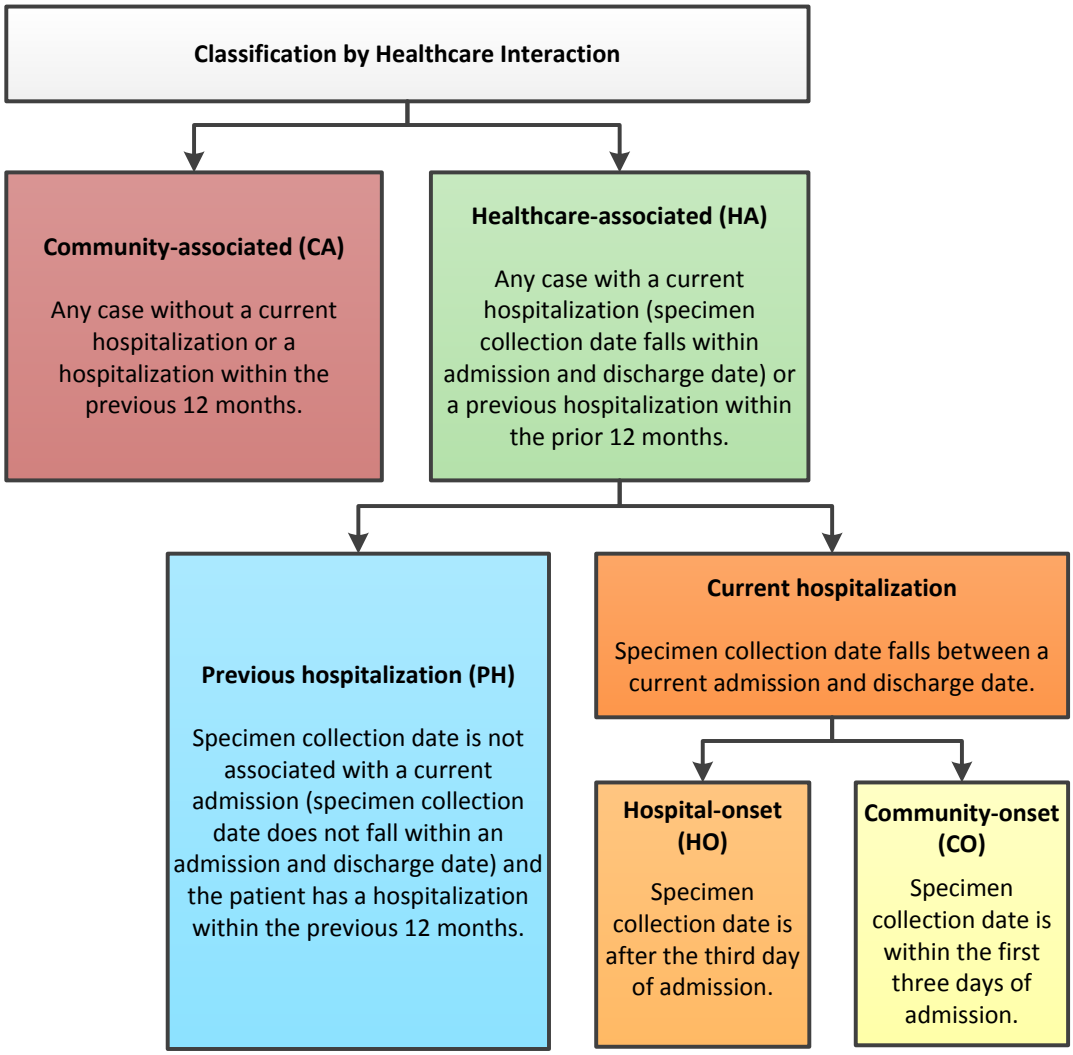
Epidemiologic Infection Classification

To evaluate all laboratory-confirmed *E. coli* infections for recent contact with the healthcare system, *E. coli* prevalence infections were matched to the Standard Inpatient Data Record (SIDR) to determine epidemiologic infection classification. Records were categorized as either community-associated (CA) or healthcare-associated (HA). CA cases were defined as patients without a current hospitalization or a hospitalization in the previous 12 months. HA cases were defined as patients who were hospitalized at the time of infection (currently hospitalized) or who had a hospitalization within the previous 12 months. Current hospitalizations were further categorized as a hospital-onset (HO) case or a community-onset (CO) case. HO cases were defined as patients with *E. coli* identified after the third day of the current admission. CO cases were identified as patients with a specimen collected within the first three days of the current admission yielding *E. coli*, indicating the patient likely acquired the organism within the community and arrived at the treating facility with it.[34] Figure 1 presents the definitions for epidemiologic infection classifications.

Figure 1. Epidemiologic Infection Classifications[a]



[a]Cohen A, Calfee D, Fridkin SK, et al. Recommendations for metrics for multidrug-resistant organisms in healthcare settings: SHEA/HICPAC position paper. *Infect Cont Hosp Ep*. 2008;29(10):901-913.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Exposure Burden Metrics

Only the first unique MDRO infection per patient per admission was used to analyze exposure burden metrics in the MHS. Admission prevalence estimated the exposure of infection at the time of admission (importation of MDROs into the MHS), which included MDROs isolated from samples collected up to and including the third day of admission, as well as samples that tested positive for infection in the prior calendar year. Overall prevalence included all individuals with an MDRO infection identified from a sample collected at any point during the admission, or samples that tested positive for infection in the prior calendar year. Admitted patients with a

history of colonization or infection were identified by searching prevalence infection MDROs from the prior calendar year to determine a history of infection. These beneficiaries were counted in both the admission and overall prevalence populations as they contributed to the colonization pressure and exposure burden for those not already colonized or infected in both populations.[34] The historical review of data is included to show a reservoir of antimicrobial resistance and pressure among *E. coli* infections. Regional rates of exposure burden were calculated as the rate of exposure (admission or overall prevalence) per 1,000 inpatient admissions per region per year.

Pharmacy Transactions

To analyze antimicrobial prescription practices in the MHS, the HL7-formatted microbiology *E. coli* prevalence infections were matched to pharmacy data to identify antibiotic prescriptions associated with *E. coli* infections in all pharmacy databases (outpatient oral (OP), inpatient oral (unit dose, or UD), and inpatient and outpatient intravenous (IV)). Prescriptions were considered to be associated with an *E. coli* infection if the transaction date in the pharmacy record occurred either seven days before or after the date the specimen was certified in the laboratory data. All pharmacy transactions, regardless of database source (UD, IV, OP), were evaluated as one data source. Cancelled prescriptions or those with zero or null filled prescriptions were removed prior to analysis. A unique antibiotic prescription was defined as the first dispensed prescription for an antibiotic per prevalence infection. Antimicrobials recommended for treatment of *E. coli* infections according to the Johns Hopkins Antibiotic Guide were retained for analysis.[34]

Antimicrobial Resistance Classification

To evaluate changes in antimicrobial susceptibility for *E. coli* infections, an antibiogram was created using antibiotic susceptibility results from the microbiology record according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.[35] The antibiogram includes the first isolate per person per organism per year from 2010 to 2015. The Cochran-Armitage trend test was used to assess patterns in susceptibility across years. Trend direction for a single antibiotic over time was established using the two-tailed *P*-value; an increase in susceptibility was denoted by a green upward arrow and a decrease in susceptibility was denoted by a blue downward arrow. A statistically significant trend was established using a $P\text{-value} \leq .05$.

Susceptibility results from the microbiology record were used to establish the level of antibiotic resistance among prevalent infections. Specimens that were non-susceptible (resistant or intermediately susceptible) to at least one antibiotic from at least three different antibiotic classes were considered MDR. Organisms that were non-susceptible to at least one antibiotic in all but two or fewer of the 17 total classes were considered extensively drug-resistant (XDR). Possible extensively drug-resistant (PXDR) infections were those organisms non-susceptible to some or all antimicrobials tested in an antimicrobial category but not tested against all 17 antimicrobial categories in the definition and could therefore not be included or excluded as an XDR infection. Possible pandrug-resistant (PPDR) infections were those that could not be definitively identified as XDR based on the XDR definition and were non-susceptible to all antibiotics tested but were not tested against all antibiotics in the definition and could therefore not be excluded as a pandrug-resistant (PDR) infection. PDR organisms were organisms that were non-susceptible to all antibiotics in all antibiotic classes in the definition.[36] Carbapenem resistance, defined as

antibiotic resistance to at least one carbapenem, was also evaluated.[37] MDR and CRE isolates were considered separately, therefore isolates could have been counted under both classifications. For the remainder of this report, unless otherwise stated, resistant and resistance are defined as *E. coli* infections having any level of antibiotic resistance, whether it be MDR, PXDR, XDR, PPDR, PDR, or CRE. See Appendix A (Table A-1) for a list of antibiotics used to identify the level of resistance among infections.

Special Populations

E. coli infections identified among DON active duty personnel were matched to the Defense Manpower Data Center (DMDC) Contingency Tracking System (CTS) to explore deployment-related infections occurring on or between the start and end dates of the deployment plus 30 days. Thirty days post-end of deployment was used to ensure all *E. coli* infections related to the deployment were included. Records with no deployment end date (i.e., service member remains deployed) were also included provided that the infection occurred in the analysis year (2015) and the start date of deployment was within 180 days of the specimen certification date.

Statistical Analysis

The MHS Data Mart (M2) was used to obtain counts of TRICARE eligible MHS beneficiaries for denominators. The annual incidence rate was defined as the count of all incident infections per year divided by the corresponding annual M2 eligible beneficiary count (represented by the count in July) per year. A weighted average of incidence rates by month for the three years prior to the current analysis year (weighted historic monthly baseline) was used to assess the seasonal component of *E. coli* infections in 2015. One and two standard deviations, both above and below the weighted historic monthly baseline, were used to indicate statistically significant changes in incidence rates of *E. coli* infections in the analysis year.

All incidence rates are presented as an estimated rate per 100,000 persons per year. Due to the transient nature of the military beneficiary population and an inability to account for the proportion of the beneficiary population that receives medical care outside of the MHS, estimated rates are used for comparison of rates from year to year. A historical baseline was created using the weighted average of the immediately preceding three years. The historical baseline of the incidence rate serves as a clinical reference for the 2015 incidence rate. Two standard deviations on either side of the baseline were calculated to assess variation in incidence rate in the three years prior to the current evaluation period. Two standard deviations provide the upper and lower bounds (approximately 95%) for assessing whether the observed occurrence was likely due to chance, and for consideration of clinically significant trends.

Results

Section A – Descriptive Epidemiology

Incidence of *Escherichia coli*

In 2015, the annual incidence rate (IR) for *E. coli* infections among MHS beneficiaries treated at an MTF was 702.3 per 100,000 persons; this represents an 18.6% change above the 2012-2014 weighted historic IR (592.2 per 100,000 persons) (Table 2). Incidence rates across all services and the active duty (AD) population in 2015 were more than 15% above the weighted historic baselines. However, the IRs across all services and the DOD AD population were within two standard deviations (SDs) of the historic IRs and thus indicate that the observed increase could be fluctuations of *E. coli* infections in these populations.

Table 2. Incidence Rate (IR) for *Escherichia coli* Infections in the MHS, CY 2015

Population	2015 IR	Weighted Historic[a] IR 2012 - 2014	Two Standard Deviations: Weighted Historic[a] IR	2015	
				Direction	Percent Change[b]
MHS Beneficiaries	702.3	592.2	157.4	↑	18.6%
Air Force	654.5	544.3	149.8	↑	20.2%
Army	732.8	619.7	162.6	↑	18.3%
Marine Corps	754.8	632.9	164.0	↑	19.3%
Navy	651.4	558.4	164.0	↑	16.7%
DOD Active Duty	857.0	731.9	209.2	↑	17.1%

Rates are presented as the rate per 100,000 persons per year.
A green arrow indicates an increasing percent change and a blue arrow indicates a decreasing percent change.
[a] Historic IR reflects the weighted average of the three years prior to the analysis year.
[b] This reflects the percent change from the weighted historic IR to the IR of the current analysis year.
Data Source: NMCPHC HL7-formatted CHCS microbiology and MHS M2 databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Demographic Distribution of *Escherichia coli*

There were 66,206 incident *E. coli* infections identified among all MHS beneficiaries treated at an MTF (Table 3). Incidence among females was nearly 11 times higher than among males. Beneficiaries aged 18-24 years experienced the highest incidence rate (1,225.3 per 100,000 persons per year) among all age groups, followed closely by beneficiaries 25-34 years old. Among beneficiary types, AD service members had the highest incidence rate (852.9 per 100,000 persons per year), followed closely by family members.

Table 3. Demographic Characteristics of *Escherichia coli* Infections in the MHS, CY 2015

	N = 66,206	
	Count	**Rate**
Gender		
Female	60,582	1,307.2
Male	5,624	117.3
Age Group (in Years)[a]		
0-17	6,605	336.2
18-24	14,167	1,225.3
25-34	14,413	1,201.3
35-44	8,676	1,040.3
45-64	14,086	675.6
65+	8,258	377.5
Beneficiary Type		
Active Duty	11,789	857.0
Family Members	47,058	852.9
Retired	4,060	187.2
Other[b]	3,299	--

[a] Age was unable to be classified in one record.
[b] Rate is not reported due to variation in population denominator.
Rates are presented as the rate per 100,000 persons per year.
Data Source: NMCPHC HL7-formatted CHCS microbiology database.
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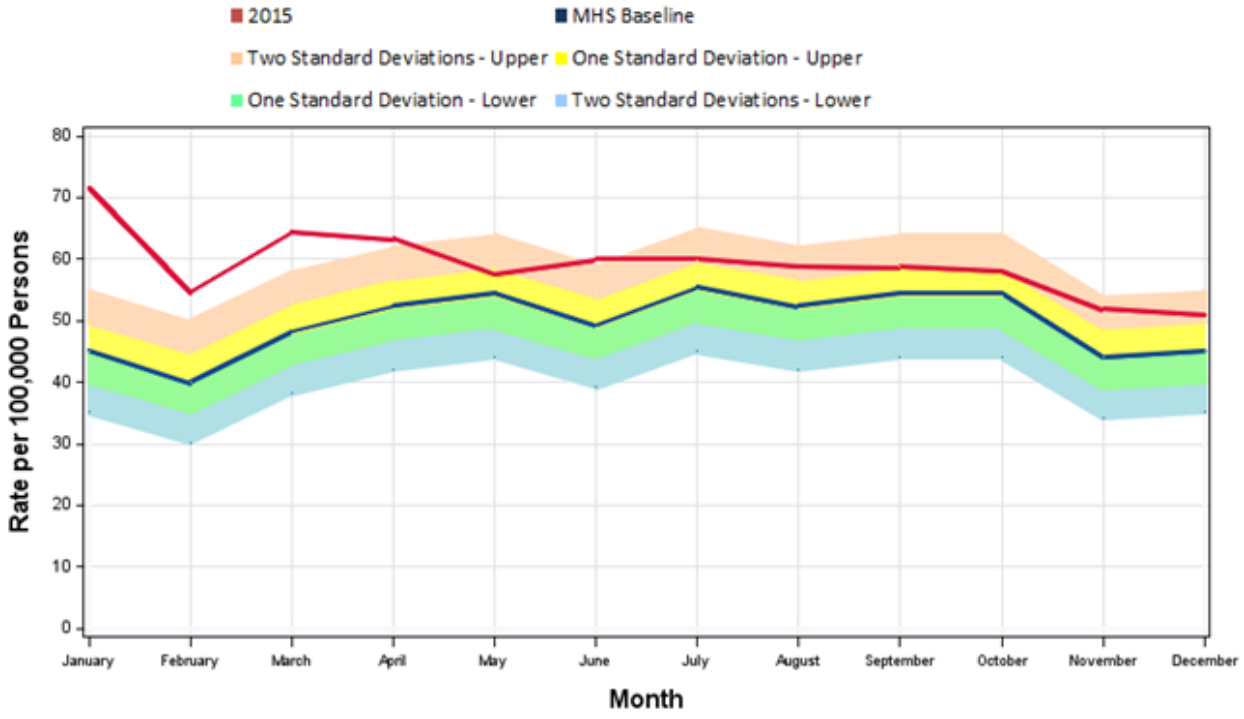
Seasonality

The 2015 monthly incidence rate for *E. coli* infections was higher than the MHS baseline (Figure 2). Monthly incidence rates from January through April 2015 were more than two standard deviations above the MHS baseline and thus may indicate a substantial increase above the historical variation of *E. coli* infections during this part of the year. However, in May and from July through December 2015, incidence rates were within two standard deviations of the MHS baseline and therefore consistent with prior historical observation. Unlike trends seen in the MHS baseline, the highest incidence rate was observed in January 2015. Throughout the summer, rates of *E. coli* infections remained relatively stable. The lowest incidence rates occurred in November and December 2015.

Figure 2. Monthly Incidence of *Escherichia coli* Infections and Baseline Comparisons in the MHS, CY 2015



Rates are presented as the rate per 100,000 persons per year.
Bands indicate one and two standard deviations above and below the weighted historic monthly baseline.
The monthly baseline is a weighted average of the three years prior to the analysis year.
Data Source: NMCPHC HL7-formatted CHCS microbiology and MHS M2 databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Escherichia coli Clinical Characteristics

In 2015, there were 75,041 prevalent *E. coli* infections among all MHS beneficiaries treated at an MTF (Table 4). The majority of *E. coli* specimens were collected in the outpatient setting (97.7%) as non-invasive infections (96.6%). Ninety-six percent of *E. coli* positive samples were collected from urine.

Table 4. Clinical Characteristics of *Escherichia coli* Prevalence in the MHS, CY 2015

	N = 75,041	
	Count	Percentage
Specimen Collection Location		
Inpatient	1,737	2.3
Outpatient	73,304	97.7
Infection Type		
Invasive	2,547	3.4
Other Non-Invasive	72,494	96.6
Body Collection Site		
Blood	435	0.6
Respiratory	220	0.3
SSTI/Wound	1,080	1.4
Urine	72,203	96.2
Other	1,103	1.5

Data Source: NMCPHC HL7-formatted CHCS microbiology database.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Exposure Burden Metrics

Table 5 presents two different metrics defining MDRO infection rates for healthcare-associated exposures. In 2015, there were 252,751 direct care inpatient admissions across all MHS MTFs. Among *E. coli* infections, the overall MDRO prevalence rate was 11.1 per 1,000 inpatient admissions; this measures the exposure of infection at any point during the admission or one year prior. The admission MDRO prevalence rate was slightly lower at 10.5 per 1,000 inpatient admissions; this measures the magnitude of infection at the time of admission (importation of MDRO into the healthcare system) or one year prior. This observation suggests that the majority of MDR *E. coli* infections were imported into the hospital setting from the community. The southern US region experienced the highest overall and admission MDRO prevalence rates (17.0 and 16.0 per 1,000 inpatient admissions, respectively). Conversely, the northeastern US region had the lowest overall and admission MDRO prevalence rates (11.0 and 10.3 per 1,000 inpatient admissions, respectively).

Table 5. MDRO Healthcare-Associated Exposure Burden Metrics among *Escherichia coli* in the MHS, CY 2015

	Overall MDRO Prevalence[a]		Admission MDRO Prevalence[b]	
	Count	Rate[c]	Count	Rate[c]
Region				
OCONUS	212	12.1	204	11.7
US Midwest	133	13.0	128	12.5
US Northeast	15	11.0	14	10.3
US South	999	17.0	941	16.0
US South Atlantic	945	11.3	912	10.9
US West	1,087	13.4	1,046	12.9
Total	2,803	11.1	2,657	10.5

[a] Overall MDRO prevalence included all individuals with an MDRO infection identified from a sample collected at any point during the admission, as well as samples that tested positive for infection in the prior calendar year.
[b] Admission MDRO prevalence included all individuals with an MDRO infection identified from samples collected up to and including the third day of admission, as well as samples that tested positive for infection in the prior calendar year.
[c] Rates are presented as the rate per 1,000 inpatient admissions per year.
Data Source: NMCPHC HL7-formatted CHCS microbiology database.
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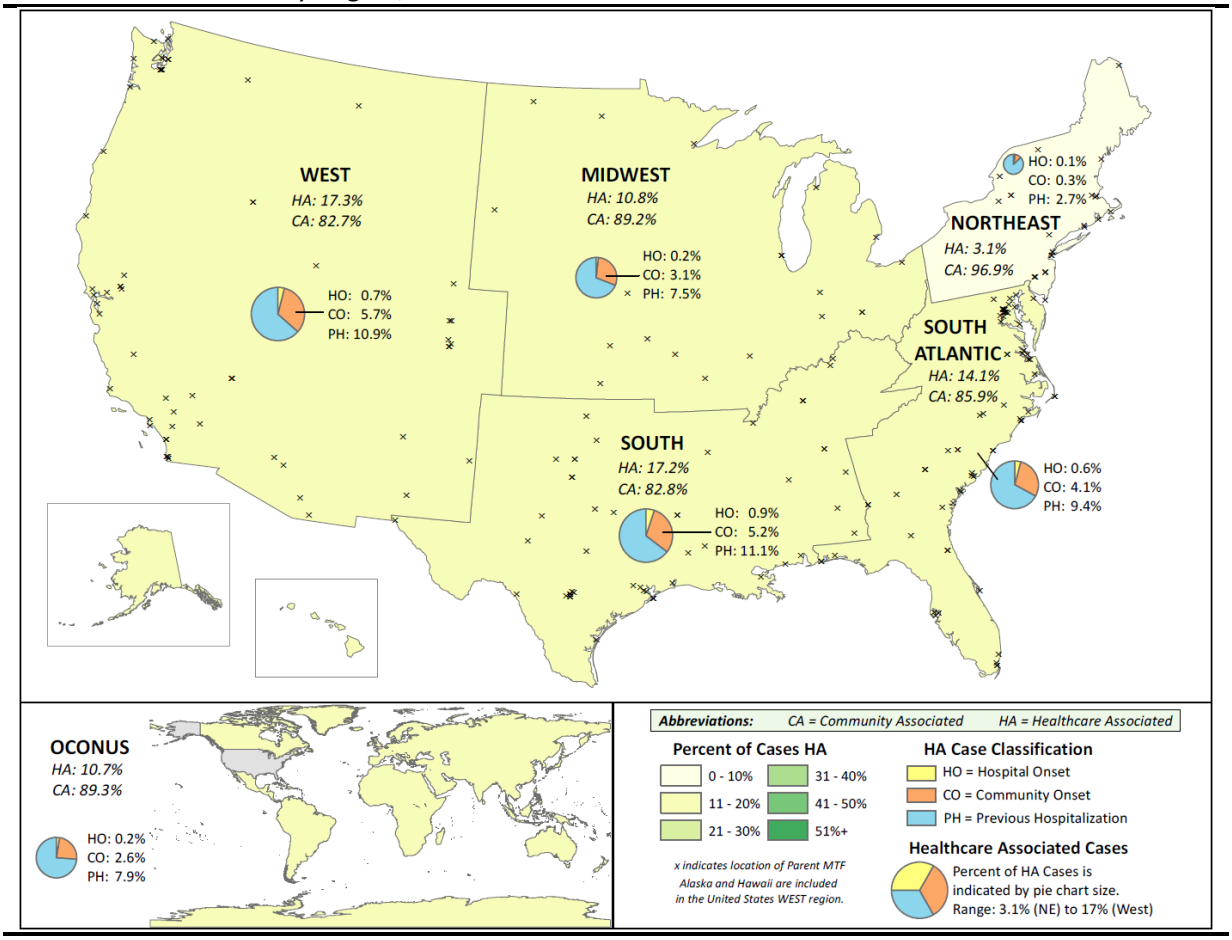
Regional Epidemiologic Infection Classifications

Among all *E. coli* prevalence infections identified in the MHS, 85% were CA and 15% were HA. HA cases in the US ranged from 3.1% in the Northeast region to 17.3% in the West (Figure 3).

HA cases were further categorized into HO, CO, or previous hospitalization (PH) groupings. Among the 11,246 prevalent *E. coli* infections identified as HA cases, the greatest proportion were classified as PH (n=7,403; 65.8%), indicating that the *E. coli* specimens were not associated with a current admission but that the patient had a prior hospitalization in the previous 12 months. The second largest proportion of HA cases were CO cases (n=3,391; 30.2%), indicating that the infection most likely originated from the community (i.e., specimens were collected within the first three days of hospital admission). Only 452 (4.0%) of HA cases were HO, meaning that the infection was identified after the third day of admission and likely contracted during the current hospitalization (data not shown).

Figure 3. Proportion of Healthcare- and Community-Associated Cases among *Escherichia coli* Infections in the MHS by Region, CY 2015



Data Source: NMCPHC HL7-formatted CHCS microbiology, SIDR, and MHS M2 databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Section B – Antimicrobial Resistance and Use

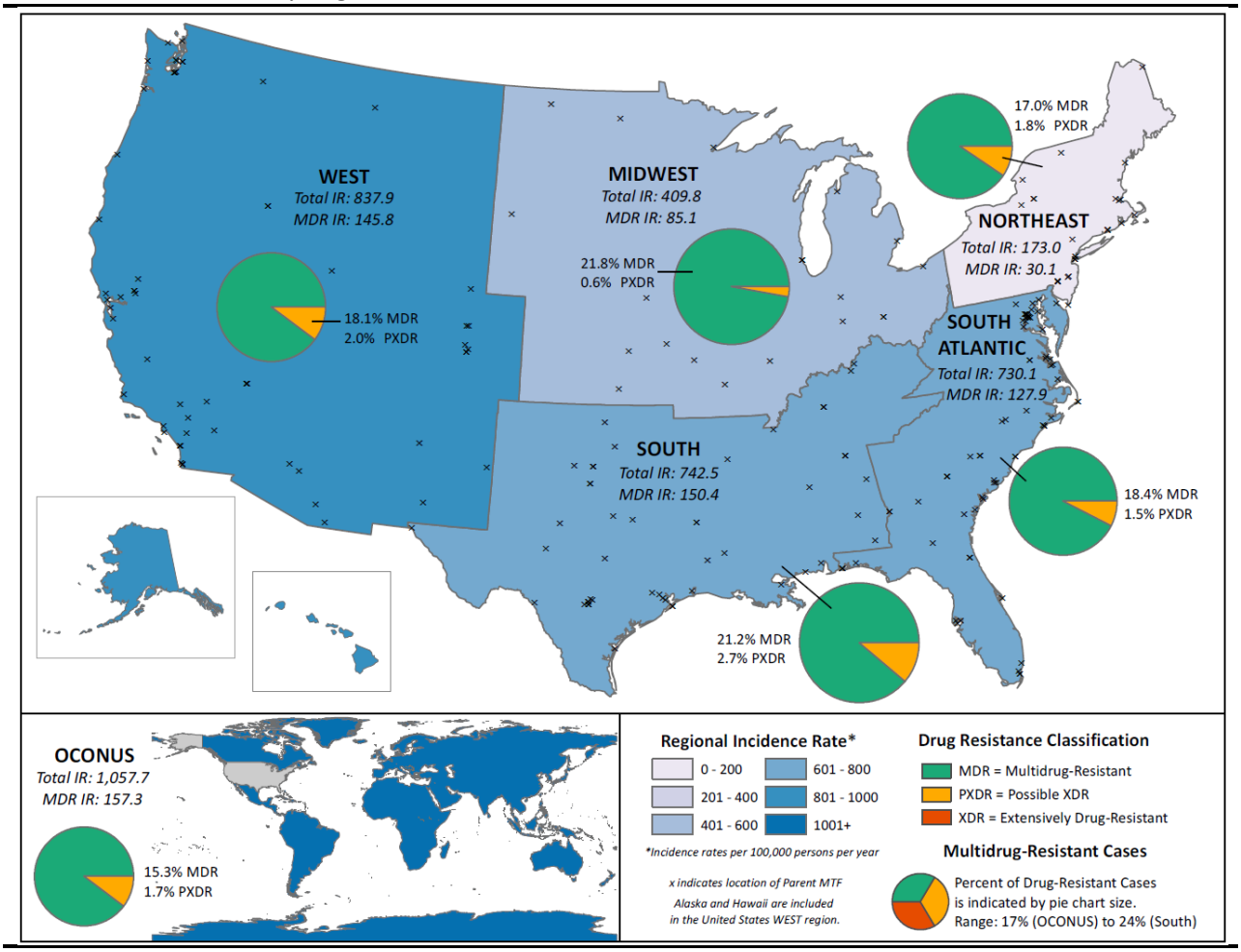
Regional Multidrug Resistance

In 2015, the incidence rate of *E. coli* among all MHS beneficiaries was 702.3 per 100,000 persons. Regionally, OCONUS locations had the highest incidence rate of *E. coli* infections (1,057.7 per 100,000 persons) (Figure 4); in the US, the incidence rate of *E. coli* infections ranged from 173.0 per 100,000 persons in the Northeast to 837.9 per 100,000 persons in the West.

Roughly 21% of all *E. coli* infections were drug-resistant. The majority of these drug-resistant infections were MDR (18.8%), while less than 2% were PXDR, and less than 1% were CRE infections. There were no XDR, PPDR, or PDR *E. coli* infections identified among MHS beneficiaries in 2015. OCONUS locations, as a group, experienced the highest incidence rate of MDR infections (157.3 per 100,000 persons) in 2015. Although the western portion of the US experienced the highest incidence rate of infections among all US regions, the southern region had the highest rate of MDR incident infections (150.4 per 100,000 persons) in 2015.

Prevalent *E. coli* infections were also assessed for carbapenem resistance. Carbapenem-resistant (CR) *E. coli* infections accounted for 0.03% (n=24) of prevalent infections; the South Atlantic region had the most CR *E. coli* infections (11), followed by the South (5), West (3), Midwest (3), and OCONUS locations (2) (data not shown). There were 17 CR *E. coli* infections in 2012, followed by 25 infections in 2013 and 14 infections in 2014, signifying variable trends over the past three years.

Figure 4. Annual Incidence Rate (IR) and Percentage of Multidrug Resistance among *Escherichia coli* Infections in the MHS by Region, CY 2015



Rates are presented as the rate per 100,000 persons per year.
Data Source: NMCPHC HL7-formatted CHCS microbiology, SIDR, and MHS M2 databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Antibiogram

Table 6 displays an antibiogram of *E.coli* incident infections for all MHS beneficiaries from 2010 to 2015. In the MHS in 2015, *E. coli* was most susceptible to carbapenems: meropenem (100%), imipenem (99.9%), and ertapenem (99.9%). *E. coli* was least susceptible to ampicillin (61.6%) and ampicillin/sulbactam (63.9%). Statistically significant decreases in susceptibility from 2010 to 2015 were observed among 13 of the 21 drugs commonly used to treat *E. coli* infections.

Table 6. Antibiogram of *Escherichia coli* Infections Identified in the MHS, CY 2010-2015

Antibiotics	2010	2011	2012	2013	2014	2015	Susceptibility Trend	Comment[a]
Amoxicillin/Clavulanate	86.6	88.0	86.9	87.3	87.5	88.0		↑
Ampicillin	61.7	61.2	60.5	61.1	61.4	61.6		
Ampicillin/Sulbactam	69.0	68.2	67.6	65.3	64.2	63.9		↓
Cefazolin	92.4	91.9	92.6	91.7	91.4	91.0		↓
Cefepime	98.4	98.1	98.2	98.0	98.1	97.6		↓
Cefotaxime	98.6	98.5	98.6	98.5	98.3	98.3		↓
Ceftazidime	98.2	98.0	97.9	97.7	97.8	97.5		↓
Ceftriaxone	97.4	97.5	97.7	97.3	97.2	96.8		↓
Cefuroxime	95.9	95.3	95.7	95.2	95.2	94.6		↓
Ciprofloxacin	91.4	90.9	90.6	90.3	90.2	89.9		↓
Ertapenem	99.9	99.9	99.9	99.9	99.9	99.9		
Gentamicin	94.9	94.7	94.6	94.5	94.4	94.3		↓
Imipenem	99.8	99.9	99.9	99.9	99.9	99.9		↑
Levofloxacin	91.9	91.5	91.3	90.8	90.3	90.1		↓
Meropenem	99.9	100.0	99.9	100.0	100.0	100.0		
Moxifloxacin	90.5	90.0	91.5	92.3	90.9	90.7		
Nitrofurantoin	97.5	97.4	96.4	96.4	96.1	97.0		↓
Piperacillin/Tazobactam	97.5	98.3	98.3	97.7	97.8	97.8		
Ticarcillin/Clavulanate	92.9	93.9	92.5	91.5	92.4	92.4		↓
Tobramycin	95.3	95.0	95.2	94.8	94.5	94.6		↓
Trimethoprim/Sulfamethoxazole	81.9	81.5	81.3	81.6	82.0	81.8		

[a] Arrow indicates the antibiotics with a significant change in direction of trend for significant two-tailed Cochrane-Armitage tests for trend established for a single antibiotic over time. A significant increase in susceptibility is denoted by a green upward arrow and a significant decrease in susceptibility is denoted by a blue downward arrow.

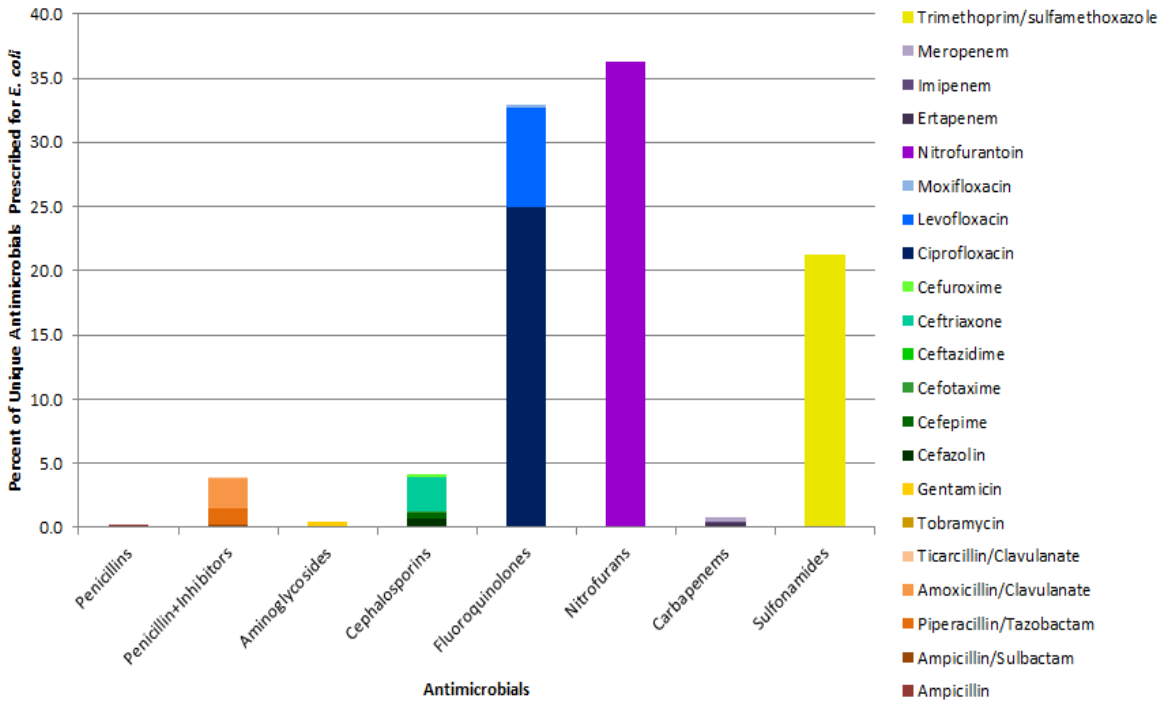
Data Source: NMCPHC HL7-formatted CHCS microbiology database.

Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Antimicrobial Consumption/Prescription Practices

In 2015, nitrofurans were the most common class of antibiotics prescribed for *E. coli* infections (36.3%), followed by fluoroquinolones (33.0%). The most commonly administered antibiotic was nitrofurantoin (36.3%), followed by ciprofloxacin (25.0%), trimethoprim/sulfamethoxazole (21.3%), and levofloxacin (7.7%). The remaining antibiotics were prescribed for less than 3% of infections.

Figure 5. *Escherichia coli* Infection and Prescription Practices in the MHS, CY 2015



Only the first occurrence of a unique antibiotic was counted per person per infection, regardless of administration route.
Data Source: NMCPHC HL7-formatted CHCS microbiology and HL7-formatted pharmacy databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Section C – Special Populations

Of the 75,401 prevalent *E. coli* infections in 2015, less than 1% (123 infections) occurred among DON AD deployed personnel. *E. coli* occurred with greatest frequency among the 18 to 24 age group (56.9%) and females (85.4%) who were deployed.

Table 7. Characteristics of Special Populations with *Escherichia coli* Infections in the MHS, CY 2015

	N = 123	
	Count	Percent
Deployed Personnel		
Gender		
Female	105	85.4
Male	18	14.6
Age Group (in Years)		
0-17	--	--
18-24	70	56.9
25-34	41	33.3
35-44	10	8.1
45-64	2	1.6
65+	--	--

Data Source: NMCPHC HL7-formatted CHCS microbiology and DMDC CTS databases. Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Discussion

The 2015 *E. coli* IR was nearly 19% higher than the weighted historic IR from 2012-2014. Although the 2015 IR was elevated, it was within two standard deviations of the weighted historic IR and therefore within the expected fluctuation for *E. coli* infections in the MHS beneficiary population. Similar increases were observed among beneficiaries in all services (Army, Air Force, Marine Corps, and Navy) and the DOD AD population; increases ranged from 17% to 20% but all were within two standard deviations of the historic baseline and therefore within anticipated variability. Although these increases cannot be validated by current national surveillance studies, an increase in *E. coli* infections was also observed in 2014, when the IR was 24% above the 2011-2013 weighted historic IR.

The highest monthly IR occurred in January and is explained by the definition used for an *E. coli* infection. Only the first occurrence of an *E. coli* infection was counted per person per year; if a person had multiple episodes of an *E. coli* infection (e.g., a recurrent *E. coli* UTI), the first of which occurred in January, the infection would be counted once in January and never again for the rest of the year, resulting in seemingly inflated IRs early in the calendar year. Monthly IRs were thus higher than expected from January through April in 2015, and then dropped to expected levels in the summer months, stabilizing and remaining within expected variation through the remainder of the year. Seasonal rates and variability cannot be corroborated by the literature, which has yet to determine a direct seasonal correlation due to the variety of illnesses and mechanisms through which *E. coli* causes disease.[7]

An evaluation of clinical and demographic characteristics found that the incidence rate of *E. coli* infections was 11 times higher in females than in males, and that UTIs were the most common clinical manifestation. UTIs caused by *E. coli* are one of the most common extraintestinal infections among young, otherwise healthy, sexually active women.[40,41] Anatomically, women have a shorter urethra than men, which lessens the distance the bacteria must travel to reach the bladder. Additionally, the female urethra is in close proximity to bacterial reservoirs around the rectum and vagina. Furthermore, *E. coli* infections among females of reproductive age may be captured at higher rates than in other populations because the Infectious Disease Society of America (IDSA) and US Preventive Services Task Force recommend screening for asymptomatic bacteriuria among pregnant women and those undergoing urological procedures.[42,43] These screening recommendations, along with natural anatomical features and other factors (e.g., dose-dependent sexual activity, use of antimicrobials, or genetic predisposition), may allude to the gender disparity of UTIs in the MHS beneficiary population.[44]

The majority of *E. coli* prevalent infections identified in the MHS were CA (85%) and urine infections (96%); this is consistent with observations in the general US population, with *E.coli* being the primary etiological agent for more than 80% of CA UTIs.[40,41] In 2009-2010, the NHSN reported that *E.coli* was the second leading cause of HAIs nationally (11.5% of HAIs), and by 2014 *E. coli* was the leading cause of HAIs at 15.4%.[21,45] An almost identical proportion (15%) of HA *E. coli* infections were seen in the MHS in 2015. These numbers, in conjunction with other data (e.g., MDR data, antimicrobial use data), confirm the need for continued infection control and antimicrobial stewardship programs.

Approximately 21% of all *E. coli* infections in MHS beneficiaries were classified as drug-resistant, among which 19% were defined as MDR; these figures are higher than what has been reported for the general US population (9.1% in 2001 and 17% in 2010).[46,47] Regions with the highest total IRs also represented those with the highest MDR IRs. Increased colonization of MDR *E. coli* strains and increasing antimicrobial pressure (through antimicrobial prophylaxis and presumptive treatment) have been proposed as possible causes of MDR *E. coli* infections at MTFs.[24,30] A lack of pathogen identification and recommended empirical treatments without prior antimicrobial susceptibility determination (presumptive treatment) contribute to the recurrence of UTIs and increased resistance.[48] As previously stated, resistant infections pose serious challenges to clinical treatment and can reduce mission readiness.[7,49-51] Strict antimicrobial stewardship, treatment using individual organism resistance patterns, consultation of local antibiograms, and patient education are advised to ensure that viable treatments remain available for *E. coli* infections and prevent organisms from increasing in resistance and/or passing resistant determinants to other organisms.

The overall MDRO prevalence rate measured the reservoir of MDR *E. coli* infection in a healthcare setting and the admission MDRO prevalence metric measured the magnitude of MDR *E.coli* imported into a healthcare setting. The admission MDRO prevalence rate comprised the majority (95%) of the overall MDRO prevalence rate. Hence, this demonstrates that the majority of MDR *E. coli* burden were within the first three days of an inpatient admission, and were thus more likely community onset rather than a result of the hospital setting. Interventions that support antimicrobial stewardship and infection control are more easily implemented and enforced in the healthcare setting than in the community; however, these results highlight the importance of drug-resistance surveillance outside of the hospital setting, where infections may be contributing to a reservoir of *E. coli* in the community.

The 2010-2015 antibiogram revealed that most *E. coli* isolates displayed high susceptibilities to several tested antibiotics. Carbapenems, a class of antibiotics typically reserved as a treatment of last resort for *E. coli* infections,[52] were prescribed for less than 1% of *E. coli* infections and had susceptibility rates greater than 99% among the MHS beneficiary population. In 2015, *E. coli* infections were least susceptible to ampicillin and ampicillin/sulbactam (61.6% and 63.9%, respectively) and rates of ampicillin/sulbactam susceptibility showed a statistically significant decrease ($p<0.0001$) since 2010. Fortunately, these two agents were prescribed infrequently (0.2% for both) for *E. coli* infections. These findings are consistent with recommendations in the literature that ampicillin and ampicillin/sulbactam should not be used as first-line treatments for *E. coli* infections due to their decreased efficacy in recent years.[53,54]

Nitrofurantoin, an antibiotic recommended for uncomplicated UTIs associated with *E. coli*, was the most commonly prescribed antibiotic (36%), and *E. coli* was highly susceptible to it (97%). Other commonly prescribed antibiotics were ciprofloxacin (25%) and trimethoprim/sulfamethoxazole (21%), which are also used to treat uncomplicated and recurrent UTIs.[55] These findings are appropriate given the high incidence rate of UTIs associated with *E. coli* among MHS beneficiaries. Nitrofurantoin and trimethoprim/sulfamethoxazole are both first-

line UTI treatment agents in the US. *E. coli* resistance to trimethoprim/sulfamethoxazole has been increasing in recent years.[11,12,18,56] However, this analysis did not find a statistically significant increase in *E. coli* resistance to trimethoprim/sulfamethoxazole from 2010 to 2015. The gradual increase in fluoroquinolone (e.g., ciprofloxacin) resistance among UTI isolates is also a concern in the US healthcare community,[21,57] and such an increase was exhibited in the MHS data. Ciprofloxacin is not recommended to treat non-catheter related UTIs in healthy adult patients due to its decreased efficacy, so further investigation of the MHS beneficiary population receiving this medication is warranted.[35,58] Prescription practices for all types of *E. coli* infections are anticipated to change over time as drug resistance continues to change, and should vary to reflect susceptibilities in local antibiograms.

This annual report summarized *E. coli* rates and characteristics in the MHS beneficiary population in 2015 and reported changes from previously identified trends. Given the association of *E. coli* with common clinical manifestations, namely female UTIs, and the recent increase in common infections caused by resistant bacteria, it is important to monitor and manage the significant risk presented by MDR *E. coli* and control the proliferation of resistance. Continued surveillance is warranted to monitor any changes in burden, susceptibility, and treatment options and to guide targeted prevention efforts.

Limitations

HL7-formatted data are generated within the CHCS at fixed MTFs; therefore, this analysis does not include microbiology records from purchased care providers, shipboard facilities, battalion aid stations, or in-theater facilities.

Microbiology data are useful for identifying laboratory-confirmed infections. However, infections that were treated presumptively without laboratory confirmation do not exist in the microbiology data. Clinical practice with regards to culturing varies between providers and facilities. Examples of situations where cultures may not be performed include confirmatory tests for patients with influenza-like illness (ILI) symptoms, or patients with superficial infections who are treated presumptively. Therefore, infections identified here may be an underestimate of the actual burden of *E. coli* in the MHS.

The data restructuring process for the analysis of clinical characteristics and antimicrobial resistance does not capture non-standard CHCS records. These non-standard records may include those containing the results of tests performed at reference laboratories or novel organism antibiotic combinations. The use of microbiology data for analysis of antibiotic resistance is also limited by the practice of cascade reporting, in which antibiotic sensitivity results are conditionally reported in CHCS to guide antimicrobial selection and treatment decisions. Cascade reporting is practiced to varying degrees at MHS MTFs.

The EDC data feed does not include records on medical encounters conducted outside the MHS (e.g., purchased care in the community) and it cannot be determined if an individual truly had no healthcare contact or other risk factors for *E. coli* infection, or if the individual had a risk factor that was not visible in the available data. Data on other factors commonly used to define HA cases were not available (e.g., presence of an invasive device, history of dialysis or surgery, a long-term care facility stay in the 12 months preceding the culture). Therefore, there may be HA cases currently miscategorized as CA cases. Without the ability to identify these HA cases, a more accurate estimate of CA cases could not be determined. Given the relatively healthy military population, however, any misclassification bias is likely minimal.

The pharmacy databases consist of outpatient non-intravenous prescriptions (outpatient), inpatient non-intravenous prescriptions (unit dose), and intravenous prescriptions (intravenous). Though treatment compliance in the inpatient setting can be assumed, outpatient pharmacy records indicate that a patient received a prescription and subsequent compliance is unknown. Due to near real-time data feeds, analysts are able to determine if a prescription was edited or canceled; however, the time difference between these events may allow for a short period of treatment not considered in this analysis. During ongoing surveillance efforts, patient treatment status may change as edited or canceled prescription records are received.

It is possible that not all antibiotic prescriptions were dispensed in response to an *E. coli* infection. Antibiotics that were prescribed within the appropriate timeframe to be associated with an *E. coli* specimen collection date may have actually been provided for reasons other than the documented infection, such as a different infection occurring after *E. coli* was isolated. However,

most antibiotics identified as being associated with an *E. coli* infection were antibiotics that are typically used to treat *E. coli*, so it is likely that the majority of prescriptions in this analysis were truly in response to the *E. coli* infection.

DMDC provides monthly snapshots of each active duty, reserve, and deployed Navy and Marine Corps service member's personnel record. Data are provided to DMDC by the service and analyses are dependent on the quality and completeness of these data. Any changes in service member status after the monthly data are extracted will not be captured until the following month. Active duty and reserve personnel records are maintained in separate databases, but activated reservists may be captured in the active duty DMDC file rather than the reserve DMDC file. Unit Identification Codes (UICs) reported for Marine Corps service members represent Reporting Unit Codes (RUCs), rather than UICs.

Personnel records for deployed service members are provided via CTS. The purpose of DMDC CTS is to capture personnel information for Central Command (CENTCOM) deployments. Additionally, deployment start and end dates are derived from the following systems and may not reflect the actual dates of deployment: Defense Finance Accounting System (DFAS), the Deployed Theater Accountability System (DTAS), the Secure Personnel Accountability System (SPA), historical PERSTEMPO files, and the Individual Personnel TEMPO Program. A country location of ZZ may represent shipboard or an unknown deployment location.

Infections may not be uniformly distributed within a spatial region; no distinctions were made with regard to the heterogeneity of incidence rates or prevalence among subunits (e.g., states, non-US countries). The choropleth maps represent an annual snapshot of infections and do not reflect the geographic movement of service members within the course of a year. Infections were georeferenced according to the locations of the MTFs where they were encountered, not according to the deployment locations or home locations of the service members. Map area does not equate to population size; parent MTF locations are displayed within US regions to convey the density of military medical facilities within each region.

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Appendix A: Antibiotics Used to Identify Resistance among *Escherichia coli* Infections in the MHS, CY 2015

Table A-1. Antibiotics Used to Identify Resistance among *Escherichia coli* Infections in the MHS, CY 2015

Antibiotic Class	Antibiotics Included in Class
Aminoglycosides	Amikacin
	Gentamicin
	Tobramycin
Antipseudomonals penicillins & β-lactamase inhibitors	Piperacillin/Tazobactam
	Ticarcillin/Clavulanic Acid
Carbapenems	Ertapenem
	Imipenem
	Meropenem
1st and 2nd Generation Cephalosporins (non-extended spectrum cephalosporins)	Cefazolin
	Cefuroxime
3rd and 4th Generation Cephalosporins (extended spectrum cephalosporins)	Cefotaxime
	Ceftriaxone
	Ceftazidime
	Cefepime
Fluoroquinolones	Moxifloxacin
	Ciprofloxacin
	Levofloxacin
Nitrofurans	Nitrofurantoin
Sulfonamides	Trimethoprim/Sulfamethoxazole
Penicillins	Ampicillin
Penicillins & β-lactamase inhibitors	Amoxicillin/Clavulanic Acid
	Ampicillin/Sulbactam

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Appendix B: Acronym and Abbreviation List

Acronym/Abbreviation	Definition
AD	active duty
BSI	bloodstream infection
CA	community-associated
CDC	Centers for Disease Control and Prevention
CDDEP	Center for Disease Dynamics, Economics & Policy
CENTCOM	Central Command
CHCS	Composite Health Care System
CLSI	Clinical and Laboratory Standards Institute
CO	community-onset
CONUS	continental United States
CR	carbapenem-resistant
CRE	carbapenem-resistant Enterobacteriaceae
CTS	Contingency Tracking System
CY	calendar year
DFAS	Defense Finance Accounting System
DMDC	Defense Manpower Data Center
DOD	Department of Defense
DON	Department of the Navy
DTAS	Deployed Theater Accountability System
EDC	EpiData Center Department
ESBL	extended-spectrum beta-lactamase
ExPEC	extraintestinal pathogenic *Escherichia coli*
GI	gastrointestinal
HA	healthcare-associated
HAI	healthcare-associated infection
HIPAC	Hospital Infection Control Practices Advisory Committee
HL7	Health Level 7 format
HO	hospital-onset
IDSA	Infectious Disease Society of America
ILI	influenza-like illness
IR	incidence rate
IV	intravenous
M2	Military Health System (MHS) Management Analysis and Reporting Tool
MDR	multidrug-resistant
MDRO	multidrug-resistant organism
MEPRS	Medical Expense and Performance Reporting System
MHS	Military Health System
MTF	military treatment facility
NHSN	National Healthcare Safety Network
NMCPHC	Navy and Marine Corps Public Health Center
OCONUS	outside the continental United States
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom

Acronym/Abbreviation	Definition
OP	outpatient
PDR	pandrug-resistant
PH	previous hospitalization
PPDR	possible pandrug-resistant
PXDR	possible extensively drug-resistant
RUC	reporting unit code
SD	standard deviation
SHEA	Society for Healthcare Epidemiology of America
SIDR	Standard Inpatient Data Record
SPA	Secure Personnel Accountability System
SSI	surgical site infection
UD	unit dose
UIC	unit identification code
US	United States
USN	United States Navy
UTI	urinary tract infection
XDR	extensively drug-resistant